Life Sciences

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I WILL BE SPENDING a good deal of time on the structure and importance of DNA (Deoxyribonucleic Acid) which plays such an important role in contemporary biological research. My colleagues in the physical sciences keep assuring me that the real breakthroughs of science and technology of the next couple of decades are going to be in biology. I am not sure to what extent this represents the universal feeling that the grass is greener on the other side of the fence and predictions of this kind, as all predictions which depend on new discovery for their implementation, are always dangerous. I need only remind you of the famous prediction around 1890 or 1892 that all that was left for the development of the physical sciences was the more precise determination of some of the physical constants, adding a few decimal points to some measurements, which, of course, was the immediate signal that radioactivity was about to be discovered. Any statement as to what the future looks like can, therefore, only reflect our present insight into current science and its developments.

I think it is true that biology is on the threshold of an immensely important revolution both from the standpoint of natural philosophy and from the standpoint of human affairs. For the first time the people working in diverse fields of biology have a sense of pulling together, of working on problems that are related to one another and of being able to ask the most significant questions at the chemical level of organization of the cell that they had hoped to be able to do over the past thirty, forty, fifty or sixty years. Much of this new outlook in biology, of this unifying theme of the predictability of the research of the next five or ten years, has come about from the sudden onrush of success in attack on the problems of the structure of the nucleic acids in their relationship to protein synthesis.

MAJOR TRENDS IN BIOLOGICAL RESEARCH

My remarks are directed to major trends in biological research as they can be discerned at the present time. In trying to think what the impact of such research will be on the world of the 1970's and the 1980's, it is very difficult to isolate biology from other aspects of science and from other aspects of our scientific culture. The technological or scientific advances that we can now predict would give us a very narrow view of what the future has in store for us. The very technique of discovery, of the way in which science is done, has itself undergone a considerable revolution.

The large-scale participation of the Federal Government in the support of basic scientific research is in itself a technical or managerial or operational discovery of immense significance for the pace with which new science is accumulating and will continue to accumulate in the future. It has meant that the universities have again become the focal point for basic scientific work. It has also, of course, raised many problems concerning the proper relationship of basic scientific work in the universitiesand in industry. We must all be very much concerned about the patterns of relationship that must be evolved in order to take full advantage of scientific innovation and to see to it that they come into the main stream of technological development for human benefit with the least possible delay. Such questions as the responsibilities of the academic and professional communities, of industry, and of the Federal Government in maximum assurance of the safety of the public have not been properly worked out. These are all issues of the most serious consequence which, of course, are bound to become more and more important as our capacity enlarges to deal with biological problems from a technological standpoint. We will have to work out the appropriate mechanisms whereby these interferences with the normal development of man, if I can use this in the most general terms, can be regulated to the best benefit of all. Suboptimization, a perfectionist answer to a partial problem, is a particularly vicious trap in human affairs.

Another development which is not biology, but is bound to have enormous influence on human biology and on the way science is done is, of course, the automatic electronic computer. The wonders of the computer age take a long time before they filter down into the research laboratory. (Characteristically, the technology of scientific investigation tends to be the most conservative.) But I think it is most unrealistic to underestimate the importance of the computer for discovery, for invention, for technological development and for daily life, and it ranks high among the premises of my own thinking of the next decades. Its impact on human biology is perhaps mainly the redefinition of human talent, which may be even more pointed than that of the industrial and commercial revolutions of recent history.

Mr. Winter mentioned *space biology* as an early point of contact between our interests. Actually I have not planned to say a great deal about this, as it is only one element, and perhaps the least predictable, of our outlook of biological research. The technological problems of supporting man in space flight are coming along with astounding success, as we know from recent flights. This has the flavor of careful and sometimes inspired engineering more than scientific discovery. It is certain that medicine will benefit greatly from the stimulus that these needs have given to life-support instrumentation. But the deeper issues of space biology refer to the search for different kinds of life outside the confines of the earth—which has been the limit of our investigation so far.

Mars, at the present time, is the one foreseeably accessible celestial target on which we can suggest, with any reasonable conviction that life may have evolved, where conditions are in any sense attractive for life. In fact, the Martian environment is most unattractive for higher forms of earthly life as they have evolved a specialized adaptation here. There is very little water, there is very little oxygen, the temperature cycle is severe. You and I would not be very comfortable trying to live on Mars although we could probably make a go of it with adequate protection. However, the conditions that we do know of (and our information here is severely limited) make it at least possible that kinds of life roughly similar to those as evolved on the earth have evolved on Mars. If so, they must have followed a completely independent pathway of evolution with presumably no communication with life systems on earth until the development of the space rocket.

This gives us our first chance at a really large experiment in biology, one which compares a life system on one planet with another. We may be in for some important surprises in regard to the way in which the fundamental bases of living matter could have developed in ways different from the way in which they have developed on earth. When you stop to think about it, biology is very much a human preoccupation and is a very limited kind of science. So far, our study of biology has been confined to one small speck of matter in the solar system, itself an insignificant speck in the cosmos; whereas physics and chemistry have had the means, to a considerable degree, of demonstrating the generality of the basic laws throughout the universe. We can look at the spectra from stars, we can watch the planets in their motion and from information of this kind deduce that the basic laws we have developed on earth are equally well applicable throughout the entire range of the universe.

We know that the same elements that characterize the earth are certainly present in all of the nearby stars and many of them can be directly demonstrated by spectral analysis of the light even from other galaxies. We can make no such generalizations with regard to problems of biology. We haven't the foggiest idea as to whether there is or is not life elsewhere in the solar system or elsewhere in the universe. We can say that we have no reason to believe that we are unique in the conditions which might have led to the possible development of life. Our knowledge of theoretical biology gives us no assurance that there is only one pathway by which life could have evolved; that there was only one set of chemical solutions to the problem of adaptation and evolution that has led ultimately to living man who represents the most advanced product of the life system on this particular planet.

Our instrumentation on the detection of life elsewhere in the solar system is fairly crude both from a technological and a philosophical standpoint. Some laboratories are making so far a too feeble effort. We have so little information we hardly know where to begin. The best point of departure that we can think of is to try to set up detection systems that would detect *earthly* life. My further remarks on terrestrial life will thus also have their application to exobiology (the study of life outside the earth). I intend to discuss the most general aspects of terrestrial life and it is certainly these that we would wish to concentrate on in our exploration of the planets.

FUNDAMENTAL UNITY OF LIFE

The outstanding theme of biology, and particularly the application of chemistry to biology, over the past three or four decades has been the growing realization of the underlying unity of life on earth. We see life everywhere about us; it is hard to get away from it (apart from getting away from ourselves). There is life in the air we breathe, in the microbes suspended in the atmosphere, in the dust that falls on the ground, in the water and, of course, everywhere about us on the landscape. We see the green plants; we see the animals eating them; we see the microbes which are eventually responsible for the decay of both of them. At first sight they are very different kinds of organisms. We don't often identify ourselves with the plants in our gardens, or the bugs on them; but more and more as we look into the basic processes which underlie the activity of each of these forms of life, we discover a *single* underlying theme. In fact, if one pulls apart the cells of which these different forms of life are composed, and boils them down in a test tube, one might then be very hard put to determine whether this extract had come from a bit of flesh from an animal, or the boiled-down residue of a bacterial culture or yeast culture, or whether it had come from a plant. This is to say that the fundamental constituents from which life is built are limited to a very narrow set of the innumerable possibilities of organic compounds that might have been tested, most of which are found wanting as possible candidates for the evolution of a biochemical system—or at best they failed on earth.

Of the materials of which life is composed, it has long been recognized that those that have the highest degree of specificity, those that are most particularly associated with life and into whose structure we must look for basic answers are the *proteins* and the *nucleic acids*. Since the convergence of biochemical analysis, which began almost one hundred years ago, and genetics which had its reflowering about sixty years ago, it has been gradually realized that the fundamental genetic material of *all* cells consisted of nucleic acids, whereas the working materials of the cell, the ones that are responsible for the implementation of the instructions that are passed on by heredity from one generation to another, are the proteins. Thus, with increasing sharpness in recent years, it has been realized that the fundamental problem of biology is twofold: one is the structure of nucleic acids and the chemical means by which they transmit information from one generation to the next—the problem of heredity. The second problem is one of translation. How is this information which consists of a linear code in the nucleic acids transmitted to the proteins and how can we build a general world picture which will encompass all of the varieties of microorganisms and plants and animals around these elementary premises as we are now beginning to do?

The fundamental strategy that seems to have evolved in the development of organisms on the earth has been the determination of three-dimensional structures by the linear code to produce the most wonderful results. The specification, point by point along a single fiber, as represented in the primary structure of the proteins, the primary sequence of one amino acid after another in a protein chain, is translated by the specifically directed secondary folding of this polypeptide chain to produce highly specific structures, the ones we know of as the proteins. It is this strategy that gives effective meaning to the reproductive functions of the nucleic acids.

For evolution to have anything to work on, it was necessary for there to have developed on earth a chemical sequence which had the nearly unique power of self-reproduction, a chemical sequence which in a suitable environment would result in the formation of polymer sequences similar in structure to the one used to seed the system. This has been an especially wonderful attribute of the nucleic acids which we have learned the fundamental basis of during the past ten years. Nucleic acids are large polymers of which the elementary unit is a backbone sugar phosphate chain. We have a sugar deoxyribose which is linked through a phosphate ester link to the next deoxyribose, to the next phosphate, to the next deoxyribose, and so forth. These chains are hundreds of thousands of units long in the actual DNA that is found within the cells of the organism. Coiled up in *each* nucleus of each of these cells are polynucleotide chains which if unravelled would be just about as long as I am tall—some 5 billion units long. This part of the chain, the phosphodeoxyribose sequence has no particular informational specificity. It has approximately the same relationship to the transfer of information that the "Mylar"*-base of a computer tape has. It provides the necessary backbone of continuity of structure on which information can be imprinted, which then can be picked up by the reading device. How is that information put on that sequence? The trick that nature seems to have hit upon in terrestrial evolution is the insertion of one out of four bases—guanine, cytosine, thymine, and adenine.

Nucleic acids, therefore, all have this common structure. They have this clear plastic backbone on which we find the insertion of the specific bases in a very particular order, so that if I wanted to specify the structure of a particular nucleic acid, I could take for granted the presence of the backbone and I could

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write a formula for as many thousands of times as I needed to write the full genetic message. Each of these letters, G, C, T, A, would refer to which one of the four alternative bases—guanine, cytosine, thymine, or adenine—was present in the DNA sequence at any particular point in the chain.

The full picture of the structure of DNA was completed by the theoretical "bihelical" model of Dr. James D. Watson and Dr. F. H. C. Crick. The DNA as it occurs in living organisms is not a simple single nucleotide chain but consists of a pair of complementary chains twisted around one another: the important bihelix around which all life is built. A good deal of evidence has accumulated that when one isolates the DNA from the nuclei of cells, the DNA consists of two chains intertwined around one another, and that at every position where we have adenine on one chain, we have thymine on the alternative chain. When one proceeds to build three-dimensional space models of these structures, one discovers a very plausible basis for this specific complementarity, around which most of the rest of molecular biological theory has been built. That plausibility is that in the three-dimensional models there is a specific fit between the molecular structure of guanine and cytosine—that there are three places where there are opposed hydrogens that can be used for hydrogen bonds between oxygen and nitrogen or nitrogen and nitrogen, respectively, in these two molecules.

Conversely, adenine has a corresponding fit to thymine. In the three-dimensional structure the positions of these atoms, either the ring or the substituted oxygens and nitrogens on the structures, are located just so that they are locked in, in this case by two hydrogen bonds between adenine and thymine. This then led to the speculation (for which again there has been very substantial confirmatory evidence) of how DNA replicates; how one chain of DNA can be copied in order to produce another chain with the same information. There is strong evidence in support of the idea that the double-stranded material of DNA as it is customarily found in its static form in the cell is pulled apart, perhaps just unit by unit, rather than completely unzipped, and that from a pool of activated forms of the four nucleotides which go to make up the polymer, one is selected to fill a particular slot which is complementary to the base that was already there in the parent chain from which we are attempting to derive the progeny. The climax of these considerations was the accomplishment of the same process in the test tube starting around 1955 by Kornberg who, in setting out to look for just such an enzyme, succeeded in finding an enzyme system which would accomplish precisely what I have described here. Given a primer amount of a specific DNA put into the test tube together with the enzyme and with a supply of the activated forms of the nucleotides, they are polymerized into polynucleotides whose sequences match the primer's. The nucleotides are activated by being *tri*phosphates; they have two additional phosphate groups attached to them in the monomer form. The condensation is a transfer process whereby a link between the monomer phosphate and the pyro-phosphate group is transferred to the hydroxyl on the deoxyribose of the next molecule. One could now accomplish this act of copying of the sequence of a polymer chain in the test tube—and there can be little doubt that this represents what is going on in the cell as the basic mechanism of heredity.

These accomplishments were something of a surprise to the philosopher of biology of the 1950's. We had, let us say in 1950, much less information about the detailed structure of genetic material than we did about proteins and I think it would have been anyone's guess at that time that the problem of protein synthesis would have been cracked long before we would even begin to get around to the problem of how nucleic acid is duplicated. In fact, just the converse has been true and it indeed was necessary to get a great deal of basic information in regard to the structure and the mechanism of duplication of the nucleic acid before we had the necessary equipment to begin to look at the problem of protein synthesis within the cell. It was far from there being a vague connection between the "information in nucleic acid and the information in the protein" as if these somehow were linked together by a telephone cable enabling them to talk to one another; there is a material connection. For protein synthesis to take place in a cell extract, one must furnish definite information as to the amino acid sequence that must be put together in forming the protein; and that information is indeed provided by the kind of nucleic acid that one puts into the system. However, the cell has created an intermediary between the protein and the primary tape, the DNA, in which its instructions are durably stored and passed on from one generation to another. It also has furnished a kind of scratch tape (in computer jargon) on which those instructions can be copied and recopied many times and then thrown away when no longer needed. This in turn has provided the basic mechanism for the regulation of protein synthetic processes in the cell. We have the information for 10,000 or 10,000,000 alternative proteins in every one of the cells in our body, but we only use a very small fraction of this information at any particular point in our own development. The regulation of these synthetic processes appears to be determined at this point of copying the information from the DNA into ribonucleic acid (RNA), structures differing only in some details from the DNA, but serving as the "messengers" carrying the DNA information.

Now, what then happens next? The picture is perhaps murkiest at just this point. We know that there is a rather intricate mechanism for the activation of the individual amino acids so that they in turn can be used in synthetic processes for the formation of the higher polymers. The free amino acids themselves would not have a very substantial free energy of reaction for the formation of the larger polymers and they go through a cycle of reaction where they are first of all reacted with ATP, and seconu, they form complexes with little chunks of another kind of RNA, the so-called soluble RNA of the cell. Its main functions seem to be twofold: to activate the amino acid for condensation to form longer chains; and second, to provide the specificity, the recognition mechanism, which responds to the messenger tape in order to locate a given amino acid at its precise place on the chain.

Now this is important enough that I should perhaps summarize. We have first of all the *genetic mechanism*, or double-stranded DNA, and this should be taken to indicate the intertwining of two complementary strands. The information is, in fact, represented in duplicate at every position; where we have *A* on one side, we have *T* on the other, so we can accurately deduce one chain if we know the other. The replication of the DNA involves the pulling apart of the strands and laying down of another one, also complementary to the one which is being copied. For *protein synthesis*, a segment of the total DNA is copied to RNA, a *messenger RNA* to be used as the template. A given amino acid is reacted first with ATP, and then becomes transferred onto a *transfer RNA* (also called soluble RNA or sRNA) which performs a very different function: the activation of the amino acid, and the recognition of a segment of the messenger RNA. The messenger RNA has groups of nucleotides, words of the message that came from the DNA. We now know from the recent exciting experiments of Dr. Marshall Nirenberg and Dr. Severo Ochoa many of the details of the coding, the correspondence of a sequence of bases in messenger RNA to a particular amino acid. This UUU in RNA corresponds to phenylalanine. Hypothetically a complementary sequence, AAA, in the sRNA just matches the UUU in the messenger RNA. So, at that place a phenylalanine residue will be placed in linking up to a sequence of previous, and then later on additional. amino acids in forming a given polypeptide in forming a given protein.

Now this translation mechanism has in fact been pulled apart; to a large extent it can be made to go in a number of systems in living cells. To a very large extent, though perhaps not completely, pieces of the system each extracted from very different kinds of cells will work together in the test tube. One other kind of RNA, complexed with protein in the ribosomal apparatus of the cell is needed for this to work. On the ribosome as a kind of machine jig, it is the conjunction of the messenger and the activated sRNA-amino acids which results in the polymerization of amino acids to form these specific chains.

By itself, a sequence of amino acids might appear to be no more interesting, basically, than a sequence of nucleotides from the point of view of doing any chemical work. It is one of the beauties of the system that the DNA, when it is in its double-stranded form, is, from a chemical standpoint, relatively unreactive. You wonder how in the world it, of itself, could ever have learned to do anything. In fact, it does nothing except reproduce itself and furnish the information from which messenger RNA is made. This in turn becomes a working material. There are, however, not just four but twenty different amino acids and when an amino-acid polymer chain is formed, it does not form a highly stereotyped structure.

POLYPEPTIDE CHAIN

By virtue of forces that we do not understand very well but which must include charge neutralization, hydrogen bond formation, and hydrophobic attractions among the non-covalent forces, a polypeptide chain folds into a very specific and definite three-dimensional shape. What would have been a long string with no particular unique quality to it becomes ravelled into a rather definite three-dimensional shape. This then permits that protein to act as a specific catalyst if it is going to be functioning as an enzyme; or react with other like molecules in forming larger polymeric aggregates if it is going to function as a structural element in the cell and form parts of cell wall or a fiber. Likewise, its three-dimensional shape that it assumes after this folding process is going to determine how it can function—if it is going to be an antibody which the cell may learn to produce as a means of reacting with a deleterious substance that may be introduced in the animal. This aspect of the strategy of development is the one that we understand the least at the present time in explicit chemical terms, but we do know that purified proteins can be prepared, and their primary structure can be thoroughly worked out as has been done in perhaps half a dozen cases at the present time. They can be placed in media at high temperatures at low salt concentration, or presence of high concentrations of urea, for example, where we have physical evidence that they become completely unravelled. Then if they are treated carefully and these external influences removed, we find that the extended chains of naturally occurring proteins will very often fold back again into exactly the same configuration that they had before and one in which their biological activity is restored. So, we infer that it is indeed the actual linear sequence of amino acids in the proteins that determines the shape into which it folds up, and the distribution of specific réactive residues like the imidazole groups of histidine, and the distribution of charges, as well as the shape, then determines how that protein is going to be able to function in the cell.

I want to stress that in evolution the cell had no way of knowing beforehand what would be a good protein to do a particular job. The strategy of evolution seems to have been unable to avoid random errors that take place in the primary message in the original storage tape. These are the mutations. These random errors will give rise to new experiments in substituting one amino acid for another in the formation of a polypeptide chain. Very often those experiments are disastrous. The protein that is formed may no longer be able to perform—even to fold up at all. This is one of the most common consequences in actual experimental work on mutations under genetic control of a specific protein. Sometimes a new configuration is accidentally discovered: polypeptide is formed that can fold up into a new three-dimensional configuration; then the cell that produces the new protein is put to a test. Does this new three-dimensional shape do anything for the cell in its present environment any better than what it had to go with before? If it does any better for the cell, if the cell has discovered a better enzyme or a better component with which to build a contractile protein for muscle or a better component for cell wall that insulates it better from its environment, then that protein and, consequently in turn, the nucleic acid in the cell producing that protein have stood the test of selection. That mutation will then be preserved. It will have conferred some advantage and we will then have a new starting point for further evolution. This may be an arrogant assertion, but the biochemists do believe that is precisely how life evolves. The polynucleotides were formed by some more or less spontaneous processes (many of which surprisingly are being worked out or duplicated, although we don't have the complete chain from one end to the other at the present time). These experiments in structure are going on all the time by this process of extensive trial and error and implementation of these trials through production of different protein. From an elementary polynucleotide we thus have had the full progress of evolution from the primordial slime, from the precellular organism which was just a lump of DNA, to the exquisite product of evolution that we are today.

This then is the background against which we must view the further development of biology during the next few decades. These discoveries have been the framework against which every major question of biology can now be restated and put again in very concrete and explicit terms as I propose to illustrate in my remaining time. For example, in embryology, we see the wonderful phenomenon whereby a single relatively undifferentiated cell, the egg, after having been fertilized, undergoes a very large number of cell divisions and gives rise to the fully developed animal. This animal consists of many widely diverse parts in which there has been a tremendous amount of division of labor. We don't find that the liver is trying to think and we don't find that the brain is trying to store glycogen or secrete bile as its major metabolic function. This in turn reflects a differentiation in the enzymatic capacities of these tissues and even more deeply in the regulatory decisions as to what parts of the DNA of each cell are going to be used. We have pretty direct evidence, although we would like to have it verified in somewhat more chemical terms, that the DNA is basically the same in all the cells of the body, that there has been no inherent alteration in the actual content of the message in the course of these cell divisions that gave rise on the one hand to the primordium for the brain and on the other hand for the primordium of the liver; instead there has been some mechanism which tells which of the total parts of the DNA are in fact going to be used to specify the protein synthesis in those cells.

THE STRATEGY OF STUDY OF EMBRYOLOGY

It is now clear that we must ask these questions not in the traditional terms that embryologists have developed in looking at slices of these tissues under the microscope and deciding that this is going to be a brain because we see some fibers growing out and this is going to be a liver because we see the cells starting to pack around in little lobules around central ducts. We must ask the question, "Is the DNA equally competent in extracts from these two kinds of cells if we put them in a test system for protein synthesis?" "Can we get the same messengers reproduced from them?" "Shall we isolate the regulators, the repressors and the inducers which will turn on and off the DNA isolated, let us say from eggs or sperm which will have all these capabilities?" These questions are only beginning to be asked and we don't have the answers yet, but they do tell us what the strategy of study of embryology is going to be. There is every reason for confidence that we are now asking the right questions.

SIGNIFICANCE OF TISSUE TRANSPLANTATION

I would like to turn now to a somewhat wider discussion of some other currently visible topics of tremendous human significance over the next years. One of these is the field of tissue transplantation. For some time many surgeons have had optimism about learning to perform the most intricate technical feat of transplanting not only small bits of tissue but even intact organs from one animal to another. Having watched such a procedure, one must applaud the immense technical skill which is involved in transplanting a limb or even transplanting a heart from one animal to another, retaining intact the normal pattern of circulation, patching up all the leaks between the tubes that have to be put together, and seeing that everything is indeed put back together in excellent mechanical order.

It does not take much imagination to realize what the impact on human affairs would be if we could replace our defective, aging, and sometimes inherently imperfect organs with spare parts. From the standpoint of the surgical technique of transplantation, of taking out one organ and putting another in its place, this problem has already been substantially solved. Well then, why hasn't this worked? Why has not transplantation been a major tool in medicine? Why do we not make strenuous efforts to prolong the lives of the people whom we value the most in our community (the ones who are able to command the technical resources which are needed to perform these feats of skill)? Unfortunately, nature has established more subtle barriers. It doesn't work because we are all individuals; we differ from one another; we have a different heredity and therefore chemical makeup in the fine details of our structure. Thus when an effort is made to introduce the tissue from one organism into another (unless these organisms are genetically identical with one another, and this can only be achieved in inbred colonies of mice or identical twins) a reaction takes place. Within a period of something like two weeks, perhaps a little longer (sometimes several months when the host organism is ill, as has happened in some attempted kidney transplantations) the immune mechanisms of the host go to work on the implant and eventually destroy it. Regardless of this, however, the self-destructive objective of this mechanism is often our guardian against attack from deleterious implants of other attacking microorganisms.

The problem of transplantation and all it can mean in terms of a revolution in medicine and in human affairs is therefore inherently one of understanding individual differences whereby the organism distinguishes its own parts and leaves them alone but rapidly goes to work on foreign material. How does it know it is foreign? Even my brother would be foreign to me if his tissue were put into my body. My cells would rapidly go to work on such foreign tissue and destroy it. This ultimately is a problem in protein specificity. Without going into the details, the mechanism of this immunity is eventually the formation of a specific protein (an antibody) which reacts with the substances introduced in the foreign material.

Beyond that we have to look at the way in which the genetic system of the cell, of the antibody-forming cell, is provoked in order to produce the antibody. Without detaining you on a detailed exposition of the theory of antibody formation, I think you can recognize that our understanding of the control mechanism, whereby cells are turned on and off with regard to the kinds of proteins that they can make, will in turn have its impact on our capacity to regulate the immune response which, in turn, is something we must learn to regulate if we are to achieve the goal of effective tissue and organ transplantation.

There have been some imperfect advances in this direction. We know, for example, that the administration of analogs of the components of nucleic acids, of 6-mercaptopurine, for example, will interfere with the normal process of protein formation in antibody-forming cells and this, in turn, can suppress the immune response and some palliation of the graft reaction can be effected in that way, but it doesn't last very long. This is a very crude approach. There's no selectivity at all in throwing just one base analog when thereby you would be interfering with the total process of new protein synthesis in all the cells of the body, but it does represent a first step in the direction that I am speaking of here. Plainly, what we must learn are the details of the specific kinds of messenger RNA that are made for the production of very specific kinds of antibodies, just the ones that are involved in the immune response so that we can attack that process and leave intact the normal properties of protein synthesis needed elsewhere in the body.

THE BIOLOGY OF CANCER

We have in a way an analogous problem in the biologically and medically important problem of cancer. The more we look into the biology of cancer and the more we think we have reduced it to its fundamental levels, the more puzzling that problem seems to be and the more elusive a comprehensive solution to the problem from a medical standpoint appears to be. We must get down to the fundamentals I've been speaking of just now. As you probably know, there has been quite a controversy as to the fundamental origin of the cancer process. Cancer is a sudden release from the normal regulation of a group of cells of the body. These cells just suddenly take off and stop paying attention to the normal order of things. They proliferate wildly, they crowd out other cells in their vicinity and their overgrowth eventually results in the loss of the organism. Now from one standpoint this is not a surprising evolutionary process—the same process of trial and error that I spoke of earlier, whereby alterations may take place in the DNA, must be taking place in all the cells of the body at the present time. Some of the consequences of mutation in body cells are going to be alterations in the regulatory mechanism which coordinates the cells and tissues of the body. When they result in a cell strain which is now free from the orderly restraint necessary for the proper integration of the organism, from the standpoint of that cell line, its further evolution is a very happy one. Those cells proliferate unrestrainedly, exactly like the weeds that can come through in our gardens. Now something has been done about it in the evolution of the organism or we would all be subject to cancer at a very early age. We do not know basically what the traditional restraints have been. We do not know what other discoveries the evolving animal has made during the course of its evolution that permits the suppression of the unhappy experiments on the part of our cells during the more vigorous part of our lifetime.

It has been pointed out that from the standpoint of the evolution of the species the age distribution of cancer will have relatively little impact on the reproductive potential of the species since its greatest incidence tends to fall at a period after the reproductive period of the individual; crudely speaking, processes of natural selection will have very little impact on the incidence of cancer beyond that age. Natural selection would have had a great impact on the development of early cancer because the biological propensity to develop early cancer would have been reproductively disadvantageous. A genetic system which allowed this would be at a disadvantage compared to a genetic system that evolved in which the incidence of cancer is altered. So there is some hope. The very fact that there is an age distribution of cancer does imply that there are regulatory mechanisms whereby these unhappy experiments can be suppressed but we don't know what they are as yet. The strategy I outlined for embryology applies directly to the cancer problem, as an aspect of abnormal development.

It must be said this picture of cancer biology ignores some of the most exciting developments of recent years; namely, the implication of *viruses* in the induction of cancer. But this difference may be more apparent than real if we also keep in mind the equally exciting developments in our understanding of what viruses are. We realize that they are also bits of genetic material. The virus is an evolutionary experiment in which fragments of nucleic acid have managed to break away from the organism in which they originated. It is just another bit of genetic material, but one which has developed its own adaptations for aggressive growth within the cell and for getting out of cells into new ones; a kind of trial and error result which is of best advantage to that particular clump of nucleic acids. Well, the same approach of asking specific questions about the intervention of the genetic material in the mechanism of protein synthesis is, in my view and that of almost all of my contemporaries, the way in which we are going to answer this and a comparable series of exciting questions in biology which are of the utmost importance in the foundation of medicine.

(INTERMISSION)

CHEMICAL STRUCTURE OF LIVING ORGANISMS

I have perhaps spent too long already at a rather elementary level of exposition when I could certainly have gone into much more technical detail about how one does these experiments on nucleic acid synthesis and their role in the genetic affairs of an organism, but I rather prefer to get over the spirit with which work of this kind is being done now. One can find the technical details in the scientific literature. The main element of this spirit that I would like to stress is the new aggressiveness and new sense of confidence, sometimes arrogance, not often enough humility, of our approach to the problem of the makeup of living organisms. It veers away from the gloomy predictions many of us made (and I might say I was among those at one time) that you really would not be able to pull a cell apart without destroying its integrative capacity, and when you did pull it apart, it would no longer tick. The cells can be pulled apart; we can learn how they work; we can isolate the protein synthetic mechanism; we can write down chemical structures for the parts; we can hope to substitute alternative structures when we learn what to do; and this is a very different atmosphere of biological research than the one that pervaded biology until the middle decades of this century.

One of the places that I would want to expound on is certainly the central place of the involvement in human affairs of the understanding of the genetic protein synthetic mechanism, the understanding of development of the human brain.

I think it is becoming apparent that our technical capacity, in fact, renders most of the physical apparatus that we are endowed with relatively superfluous. I'm not arguing against exercise as a necessary basis for healthy life and this indeed might turn out to be a very serious limitation on some of the rest of what I'm going to say. But people nowadays can get along very well hardly lifting a muscle. This is in some respects unfortunate. I am not necessarily advocating some of the things I'm predicting here but there is little doubt that the further progress of mankind depends not on his personal brawn but on his brain. His brain permits him to design the machines that are going to do the work for him. He can put together the steam shovel, and put together the computer that will design the steam shovel, by using his brain and amplifying his working capacity many hundreds of millions of times. Well, I think we must take this into account in considering what the further directions of evolution are going to be and what we may endeavor to do about the actual nature of man himself. This is just to point out the obvious, that the place we are certainly going to focus on is his *intellectual* capacity.

THE PROBLEM OF EUGENICS

Now as a geneticist, the problem of eugenics is often put to me and one can hardly avoid it—what is the impact of our knowledge of genetics, of the extent to which the qualities of mankind are controlled by an inner makeup that he has received by heredity, on the direction of human affairs? Should we make a specific effort to breed better men in the future? Should we take drastic means to prevent the accumulation of harmful genes which are now allowed to accumulate under the conditions of relaxation of natural selection; for example, medical care?

There are many diseases that were once relatively incapacitating, that reduced the reproductive potential of people, which have a genetical basis but which we can now alleviate. By alleviating them and permitting the reproduction at a normal rate of individuals carrying these genes, these genes are no longer held in check. They are bound to accumulate and rise in frequency. The very means that we have for permitting the normal development, for example, of children with a block in phenylalanine metabolism which in past times gave them very severe retardation in mental development now permits them—through the diets we now have—to mature reasonably normally and to reproduce and pass on their genes, and we have no specific social measures to really discourage such people from reproducing. I am not suggesting that we should discourage their reproduction; I am just pointing out that this does pose a further penalty on future generations of mankind—the necessity of maintaining these medical measures to continue to support the "defects" which in past times were minimized through the much more drastic measures of natural selection. The general answer that I have come to in viewing the problem is that it would be, in fact, premature to invest very much effort in consideration of selective breeding of the human population for several reasons: the first and most important, and one that most of my genetic colleagues have certainly agreed with, is that we do not know enough about the details of the genetic control of specific traits; that even if we knew what the most desirable traits were, we would be rather puzzled how to pursue any effective program of improvement by selective breeding.

The heredity of intelligence is a very controversial affair. We could propose selecting consistently for it, at least reversing the apparent trend of selection against intelligence in terms of reproductive rate in present-day Western society. We just do not know what the consequences of such selection would be. We don't have the information that would permit us to write the engineering specifications of the program. Before embarking on such a program, we would want to know what the costs would be, what the expectations of improvement would be generation by generation. We would want to have some confidence that any measures that would be adopted would be likely to have an impact within a reasonable period of time. What the answer is at the present time, we do not know. We have a vague idea that there is an important hereditary component in intelligence as we measure it now. We don't really know how to measure intelligence very well in the existing generation in such a way that makes it very applicable to human affairs at the present time, much less to try to predict what aptitudes of intelligence are going to be important in future times, and still less to try to project from this the details of what the improvement expected from selective breeding might be. We would not embark on programs of intensive selection in any cultivated animal or plant with the level of information that we now have for the human species.

So, whatever one thinks about the ultimate desirability of eugenics, there is no question but that our first requirement is the accumulation of much more sophisticated and detailed information about human heredity—detailed, quantitative, hard nuts and bolts kind of information—so that one could write the blueprint and not just very general schemes for it. Then we could worry about how one achieves the social implementation of any program of this kind. However, there are perhaps even more deep-seated reasons for my own preference for deferring this particular problem of human *heredity*. There are much more timely short-run measures that we haven't begun to explore by way of the modification of human *development*. We have just barely begun to scratch the surface.

MODIFICATION OF THE BRAIN

I would like to put particular emphasis on an area that will deserve much greater investigation than it has had. Perhaps the main thing you may learn from what I have to say (what has surprised me) is just how little work has been done in this direction. This is the modification of the development of the brain. In human evolution the size (perhaps in the most general sense we may think of the complexity and functional capacity) of the brain has been limited by factors which may be extraneous to the present situation. The most compelling of these is probably the size of the pelvis. The head of the infant could not be very much larger than it is without a very considerable anatomical reconstruction of the female skeleton or there would be even more frequent accidents of delivery than there are now. Birth injuries to the brain are frequent enough at the present time that you may say we have already passed the threshold of safety with regard to the extent of cerebral development in the developing fetus. We could not tolerate a very much larger incidence of birth injury during delivery without a serious social and reproductive penalty and this, therefore, would necessarily have discouraged any bold experiments that the genetic system might have undertaken that could lead to substantially increased brain volume. Now over a long period of time this would have adjusted itself.

Over a long period of time, the experiment of the "larger" brain might have evolved along with the change in the pelvis and could respond to natural selection. Instead, man has evolved in a little different direction. Instead of the pelvic aperture getting larger, man's evolutionary adaptation to this situation has been the development of the kind of brain that can learn surgery. We have the technique of Caesarean section as a conceivable means of bypassing what would otherwise be a very long step in reconstruction of the human organism. This is very simply and crudely put as there are many other things we would have to learn to do before we could get around that particular bypass, but I want to stress that there are some reasons in the natural evolution of man why he is the limited miserable creature that he now is.

I think we have to keep in mind (we shouldn't minimize the success man has made) the demands that have been put on human capability in past years. I should say, as a matter of fact, that I think it is remarkable that he has the kind of brain he does have. Consider that he evolved the brain that was able to learn Greek before Greek was invented. This is one of the main puzzles of human evolution: how man got that far without more stress, without more testing, without more compulsion for the development of the intellectual capabilities which really could only be taken advantage of after the event; when that kind of brain had been around for enough generations that we had developed the society and we had developed the social inheritance; when we developed education and schools; when we developed the library of information with which to fill that brain. This is a major puzzle. I just have to leave it at that, but it seems likely that even the Neanderthal man had a cerebral capacity not very different from ours and yet had nowhere near the kinds of demands we now make on our own brain. Or is our social maladaptation the evidence that we have used up all the margin of safety in our intellectual endowment?

Now how can we take advantage of our hopeful insight into past limitations on cerebral development? Well, first of all, we ought to take advantage of some very unhappy lessons that nature provides us—the accidents of mental retardation, the natural experiments which are often the basis of clinical advances. From these we know of a number of genetic and environmental influences that are capable of interfering with the normal development of the brain. But much more sophisticated biochemical and developmental studies on normal development are needed to exploit the hints from these diseases. Some of the most obvious kinds of experimental effort to try to get "larger" brains in experimental animals have never been attempted. But I will predict that within ten years we will know the basic facts necessary for very substantial changes in cerebral capacity and if we knew how to translate those facts in terms of human affairs, we really would have passed the threshold into another biological revolution, where we had begun a process of active modification of man himself. Plainly we have not given much thought to what this means in terms of human affairs any more than we had given very much forethought about what the impact of atomic energy would have in the kind of world we are in now. I hope it doesn't leave us in the same kind of mess!

This suggests what we might think of in terms of a long-range strategy as a substitute for eugenics. Basically we try to understand what we are about. We are on the threshold of learning how to achieve very far-reaching modifications of normal development by experimental means. When we get at cellular repressors, when we get at the nucleic messengers which are responsible for the formation of particular products, we will unquestionably know how to modulate the development of the organism in very far-reaching ways. I mentioned the brain as a crucial example of these prospects. That understanding can let us isolate the very specific biochemical and architectural features of the developing organism which would have to be manipulated in order to achieve substantial changes. Then on the basis of this understanding and the kind of short-term experimentation that experimental embryology permits in modifying the organism, we could lay out a program for genetic improvement. Because instead of having the vague objective of saying let us produce better men, we might have the very specific objective of saying let us increase the output of pituitary growth hormone during the seventh through the ninth week of gestation—not sooner and not later because that is the critical period for the development of the brain and if we turn it on during that interval we will get cerebral enlargement and we will not get some of the other possible consequences of overactivity of the pituitary. Now I have given you an example which is crude and is almost certainly wrong because we don't have the *specific* facts in which to make that model right. We substitute the right terms and the right times and the right modes of action of the regulatory substances, and I think a proposition of that kind is going to turn out to be correct. It is only the substitution of specific chemical structural developmental information for vague functional goals that is in fact going to let us think about manipulating these ends.

There are some of us, and I am not sure I don't belong to that group, who look with some alarm on prospects of this kind as we have no idea what is going to come out of Pandora's box. I think there is no use saying that it is not a good thing to do, although I think some vague fears of this kind probably are responsible for the remarkable paucity of work in this area. But it is going to be done whether we like it or not. We could say the same for atomic energy for the same reasons on a much larger scale. It is incumbent on us to understand these developments and to be giving the widest possible forethought to the impact that they are going to have on the very constitution of the human being. I think this might be an appropriate point to close the formal discussion of the program. I will be very happy to continue on the basis of explicit questions.

QUESTIONS AND ANSWERS

Q. What can you say about the relation of nutrition to these things you have been talking about?

A. Nutrition can be thought of as the *general* background against which these more selective experiments would operate. Good nutrition is a fairly recent experience for the species, and plainly has already had a great impact on the physical nature of man.

Q. Did you say you would be reluctant to apply selective measures because of what little is known about human *intelligence? What do you visualize in terms of biological technology within the next twenty-five years or so?*

A. Well, I have already made one prediction and that is that we would be able to control the size of the brain. I am not saying this will actually be done in man during the next ten years through prenatal manipulation of some kind. I do think within the following decade we might expect to have a biochemical assay for intelligence, in the sense that we would have enough insight as to what the actual storage mechanisms, what the switching mechanisms are; what is needed to make them go; that we can do what we cannot hope to do now: take a biopsy sample from the brain and make some prediction as to what the intelligence of that individual was from not only morphological but biochemical study. On that basis I think we would have the technological base on which to achieve a program of further selection. Any eugenical program faces the problem that almost every factor that we would like to modify is under rather complicated control. It would require the interplay of many different elements that have to be together at the same time, at the right time, and at the right dosage to work. The necessity of having a big enough pelvis in order to allow a big enough brain is a crude example of it. For that reason we have to dissect the elements so that we can separately estimate the value in this particular direction in order to know what to put together. I think that in twenty-five years we will have the biochemical basis for this kind of program.

Q. From the floor. (Unrecorded)

A. The inquiry had to do with the technological status of the determination of sex. Sex in mammals is determined by which of two kinds of male germ cells, spermatozoa, in fact succeeds in fertilizing the ovum. They are normally produced in about equal numbers and they are distinguished by the fact that one class of sperm has twenty-two chromosomes plus an X chromosome, the other class of sperm has twenty-two chromosomes plus a Y chromosome, these classes producing female and male, respectively. So there is about a 2 percent difference in the total amount of DNA in these two classes of spermatozoa, as well as some qualitative differences in the actual chromosome content of the sperm. The question is how to control either the formation of these two classes of sperm cells or their subsequent separation so as to control the sex of the offspring. In fact, several workers have claimed success in this direction—V. N. Shreder of the Soviet Union (Gordon of this country has claimed to have confirmed those results) in a very crude way by the electrophoresis of sperm of rabbits to achieve unisexual litters which were all male or all female depending on whether they used the sperm that migrated to one or the other pole in the electrophoresis cell. The original experiments here seem to be unassailable. On the other hand, others have attempted to repeat them and have had much less striking success. I won't say they have had no success and I think the results have been almost significant. Again, very little work has been done on a problem of this kind.

I think you would be astonished at the very low level of effort in considering the possibilities we have now for electro-optical instrumentation that could stand up cells one by one to do DNA assays on them, killing off one type and not the other or do other types of micro-analytical determinations on the particles one by one. I conclude that even if the existing reports are incorrect we in fact know enough already about the system to have a sound expectation that we would be able to make it work. I know of almost no one who is seriously working on this field; I mean using the full weight of existing technology to try to solve it. As an engineering problem it should be rather easier than discriminating enemy missiles from meteorites and intercepting them.

Q. What correlations exist between physical size of the brain and intelligence?

A. That's a rather controversial question. It is obvious you can have a large brain or a large skull with a lot of water in it and I think one would not be able to make very systematic predictions from autopsy material at the present time. There's a very nice discussion on just that point, by the way, in an article by Fred A. Mettler in a book on "Culture and the Evolution of Man"* which I strongly recommend for this kind of discussion. High I.Q. material is a little bit hard to come by for post-mortem examination and at the time it is available you have no assurance that it was at the peak of its performance. The size of the brain does change with period of life. There are also correlations with the size of the individual.

Brains of important people have sometimes been preserved and the weights of those brains depend on the fixative fluid—they may have shrunk, they may have swollen—and then they are compared with the weights of a random series of material that has freshly arrived at the morgue. The comparisons are almost

*Editor, Ashley Montagu—Oxford Press, Galaxy Books (paperbound) worthless. There is a certainty that two brains properly hooked together are better than one (or there would be no excuse for any committee—but I don't rely on that analogy) and that there ought to be some technique of enlargement of the number of cells and right kinds of cells in their connection which would let a bigger brain function better than a smaller one. We certainly do see at the extremes of the distribution that very small brains are incapable of proper function and I think we can draw some conclusions from that. I would hasten to insist that brain weight alone would not be a desirable thing to select for at the present time. We would have a very large population of hydrocephalics. That's precisely why we need a better biochemical measurement.

Q. Is there any possibility of improving intelligence by education? Nutrition?

A. I'm glad you raised that question. It ought to be possible and there are two directions that one can think of. All of what I've talked about might be analogous to looking at a computer and seeing how to make it bigger and better by changing the hardware. You suggest this might be done by changing the software, the input program formats. Actually we have been doing a good deal of both. Advances in obstetrical practice and especially in nutrition have enabled our children to grow under much better conditions for their own cerebral development. The specialized diets that we afford the extreme members of the population (e.g., phenylketonuria) illustrate the principles that must also be going on with the normals where they are not so clearly discernible.

We do not have factual information to tell us what kind of program of control of the relative growth of the brain with the rest of the body would be most advantageous for the development of intelligence but there must be such programs. Certainly during the formative years—between one and ten years of age—is where we would have to look for the full impact of such considerations. Also, there is the related question of nutrition and hormonal control of brain development. Man is unique because so much of his development of the brain takes place after his birth. This, of course, is a necessary basis for educability. That learning is the further development of the brain under the possibility of the impact of external stimuli. Most animals come out with a fairly mature brain and have limited capacity for additional modification of the internal structure.

Trying to design the educative process on the basis of present knowledge of brain function is a bit like knowing fragments of a few artificial languages on computers. Without really knowing how they can be made to communicate with one another at the machine level we try hit and miss to transfer a program to another computer. If we knew the elementary mechanism of computation in the brain I think we could get right to the problem in much more direct terms. However, I think there are some directions that should be fairly obvious by way of software in the optional use of the brain. We have some immense computational capacities. If I take two black boxes and put a man inside of one and a computer inside another, there is one class of problem that I can give which would let me tell very quickly which is inside which box. If I give a rather intricate mathematical problem on punch cards and if I get an answer in 34 microseconds, I know that box has the computer. But if I write "Tell me two plus two" in handwriting, especially if I scrawl all over the page, and I get back "four" at all, that box contains the man. Optical reading machines have been studied for years but few computers can read characters displayed in different type formats. It will tie up the entire memory of the computer to figure out the different ways in which the letter might be printed. And if you give it bad handwriting, I don't believe the problem will really be solved at all, certainly not by any present machine. We do it very well. We get some benefit in reading one another's handwriting, but I am a little concerned whether this is how we ought to use up our memory store. It is a little bit like having a system which is 99% compiler in order to adapt an outside program to the machine language of the system and only 1% is for material content.

One direction we ought to think about if we want to improve our basic capacities is to imitate the computer to a degree and standardize our communication system. If we did not have to read handwriting, if we did not have to read print in all kinds of size and shape and fonts, if we all spoke with harmonic measured tones which could be represented objectively on the oscilloscope, if our medium of communication was so standardized that no computational effort was needed to translate from one format to another, we would have a lot left. Now we can't push this principle to the ultimate absurdity. If we push it even a little bit, we dispense with poetry completely. But I think we ought to think about using it to some extent. This, of course, has been the power of the mathematician, that is, by having the most exact formulations, the most complicated formulations in abstract terms, by using a very compact notation, by using an objective language so that there would be no ambiguity about it in translation from one brain to another, a very complicated result could be transmitted with very high efficiency from one computer system to another.

Our normal language doesn't develop this way. It hasn't evolved that way in the first place. Our scientific communication is not ordinarily on this basis. Just think what you go through when you read a scientific paper in order to extract the meaning out of it, how often you end up with a reduced page of notes which conveys all the meanings that it has for you in a rather lengthy dissertation. (I shudder to think what a short page is going to be needed to take home today's meat!) But if we had sufficiently standardized media for communication, the notes would be all that would have to be presented. They would mean the same thing to each one of us. We would have had the same connotations from them all and we could spend our effort of individuality at higher things than just getting to know the other fellow. I mean that rather seriously. It can be pushed too far. There are serious limitations. There are enough genetically controlled variations in our cerebral content that standardization isn't going to work at quite the same efficiency as having a common compiler program for two IBM 7090 machines in use across the country. I am sure we have not pushed it enough and I think certainly some standardization of the means of presentation of information could save us a tremendous amount of computational effort.

Q. Would you care to comment on the effect of fallout on genetics?

A. If I take your statement literally, my tongue-in-cheek answer would be, "It has had a tremendously stimulating effect and certainly has brought about public awareness of the subject of genetics." Fallout, of course, does represent a means whereby the natural rate of mutation, these trials and errors in the substitution of one base for another in the DNA, occurs at an increased rate and the long-term impact of this can hardly be anything but deleterious.

We have enough mutation going on now to satisfy any foreseeable needs and to provide any amount of genetic variety that we are concerned about. If we needed more, we would have the means to produce more at the time we needed it and intentionally. I think one has to look at this with some perspective that the discussion about fallout at present levels has concerned differences that are only a small percentage of the naturally occurring mutation rates. If one is exercised about the total number of unhappy lives that are generated by the occurrence of these accidents, and I think one should be exercised, one must also be exercised about many things that we are doing to our environment that may have comparable consequences. There are probably many constructive measures to *reduce* mutation rates that we do *not* take. We know that there are chemicals which in an experimental system will alter the "spontaneous" mutation rate and one might argue that it is just as reprehensible to refrain from looking at the ways of accomplishing a reduction of the mutation rate in man, if mutations are evil, as it is to spread more radioactivity or other chemicals around. But saying that one thing is black, doesn't whiten everything else.

Q. Referring to some other point that you already made, what is the outlook as far as understanding of the fundamentals of aging and alteration of the life span?

A. I wish I knew more about this personally. It is a field that has begun to wake up in the last few years. My own point of departure is that aging is *not* a fundamental cellular phenomenon in the most part, that it is a process that involves the whole organism rather than the individual cell which could renew itself. Now that can't be altogether true. There are time-dependent insults that will accumulate in rapidly reproducing cells, and so the *ultimate* limitation to the life span of an organism may indeed be cellular aging. But I just don't think that comes in nearly as soon as the aging of the body as a whole. This is an encouraging outlook because there may be more hope in solving some of the specific problems of the aging of the body than there might be in the more general one of the accumulation of noise in the information system, the scratches on the storage tapes so to speak, within the cell itself. On this view aging is comparable to the accumulation of scale and corrosion on a pipe rather than the errors in the blueprints for the piping system. If we knew of ways in which we could dispose of the scars, we might very well have gone a long way toward solving the problem. Our scars aren't routinely disposed of. We are left with fibrous residues of past history and experience, of injury and vascular breakdown throughout our bodies. This is another way of saying that collagen and its synthesis in the connective tissue framework of the body is, of course, the place where the biochemistry of aging is concentrating its study. There are certainly differences in the chemistry of young and old collagens that look very promising as points of attack on the problem. The way in which that problem can now be phrased in order to attack it more concertedly is to ask if there is any difference in the DNA or in the messenger RNA of a fibrous tissue cell as between an old and a young individual. If there is, then we know that there is a deep-seated change within the cell which is responsible for these differences and we may have a lot more trouble rooting it out. If there is not (I won't make a prediction on this)—then the problem is at a very different level and we have the challenge of finding ways to accelerate the turnover of our existing collagen.

Q. Do you have any comments to make on the kind of experimentations involved in determining genetic effects, if any, of drugs—antibiotics, that sort of thing?

A. The question was the type of experimental program which is needed to evaluate the genetic effects of chemical agents used by man. Well, that is a subtle problem and I might illustrate it by pointing out that we have no experimental evidence that *any* agent causes mutation of man. I want to stress the word *experimental* though we don't have any serious clinical evidence of this either. The human species as it now stands is already so variable having accumulated such a long record of variation, that even the very large "experiments" at Hiroshima and Nagasaki involving many tens of thousands of people have not given any unambiguous evidence of genetic effect. We are unlikely to obtain conclusive evidence in man even for agents like radiation about which there can be no doubt at all. They do affect man but the statistics of the situation are such that we are simply unable to collect experimental evidence of it in that kind of material.

We can grow colonies of tens or hundreds of thousands of mice and ask whether chemicals or radiation are effective there. It is barely possible to prove that radiation and, to some extent some chemicals—the most active mutagenic chemicals—are mutagenic in mice. We can get some quantitative figures from this to relate the mutagenic effect of these agents on mice with other experimental material. It takes a very large effort to prove the mutagenicity of any active mutagen in that material. Here we run into a very serious problem. Doses that we wouldn't dream of exposing ourselves to, which taken over the whole human population would be disastrous for the future of the species and the equivalent of a hundred rads per individual per year, are very difficult to evaluate in experimental systems. Doses of 100th of that amount, one rad per year, can by calculation, by rigorous extrapolation, be assumed to have serious deleterious effects on the human population. There would never be any hope of picking this up in an experimental system for the very simple reason that we are talking about a population of over two billion organisms (three billions very soon) for the human species; in our experimental material with great effort we can study only some hundreds of thousands of individuals in the mouse and have a limited capacity to recognize all the possible kinds of mutation that we may feel are very serious in man. How would you know about something that gave rise to mental retardation in a mouse? There's quite a technical problem of extrapolation that it would require experimentation over many generations in experimental material to get the full weight of accumulation of mutation. So we are up against a very tight nut here. We can go further, we can use simple organisms as experimental material, we can look for production in mutations in microorganisms and here, where we have very delicate tests for production of mutation, we run into the very disturbing finding that all of the things that we know are mutagenic for higher organisms are mutagenic for bacteria, but so is almost everything else to some degree.

It is very difficult to find situations which have absolutely no effect on the mutation rate on the microorganisms growing in the test tube. I might mention, for example, caffein as being a significant mutagen in microorganisms. The kind of dose of caffein that I drink every day would, by extrapolation, be equivalent in its mutagenic effect to something like one rad a day of X-radiation, which would be an intolerable dose if it did have this mutagenic effect. It would just about account for the total mutation rate, if we consider that throughout history man has been consuming caffein or other alkaloids.

I don't think we can reliably extrapolate the rate of mutation we get with the chemical treatment of one organism to another, but it would be much more dangerous to assume that this is completely incorrect; and even something like caffein cannot be totally ignored in this context. There is another approach to the problem and that is to try to find out the biochemical mechanism whereby these mutagenic agents work and to see whether these mechanisms are operating in respect to the given treatment. In microorganisms, for example, the uptake of nucleic acid analogs can be very effective in producing mutation at very high rates. We can follow the biochemistry of this with some efficiency. We know, for example, that 5-bromouracil (an analog of thymine with a bromine atom here in place of the methyl group) behaves very much like thymine in the metabolism of the cell; we can readily deceive the organism into accepting bromouracil in place of thymine in the structure of the DNA. The consequence of this is a DNA which is much more thermolabile than normal DNA and at moderate temperatures the bromouracil DNA breaks down, generating quite a high mutation rate. Now we do not know that bromouracil is mutagenic in higher organisms and direct proof would be hard to get. But it is taken up in DNA and I wouldn't eat any of it.

Thus we face a very difficult problem: one of immense subtlety in testing materials that might be mutagenic for their impact on man. The only sensible outlook that I can see is to try to understand the biochemistry of action of these things, to be very cautious about agents that have known chemical effect either on DNA or which interact with the biosynthetic mechanism for the formation of the DNA within the cell. One general way of following this (as we do in the case of bromouracil and other analogs) is use of radioactive isotope determinations to ask whether the material that we are concerned about finds its way into the nucleic acids of the cell. For if it does that, then it surely has the potentiality for spoiling a normal function of these particular polymers.

Furthermore, agents can be mutagenic without actually becoming part of the genetic material, they may *externally* modify the normal process of DNA synthesis and these would be somewhat more subtle but, again, we have the biochemical means for investigating this.

Q. From the floor. (The question concerned the physical understanding of the subjective personality.)

A. The answer may depend on what you mean by understanding. It is the subjective man who is claiming to understand the subjective. When you put this kind of question to a scientist he has to stop and ask exactly what you mean by it and he will end up with the usual dictum about causality: that if I know enough about the present state of the system and I understand the laws of the system, I will be able to predict the future state. On those terms the answer is in principle "Yes". But as in many real situations it is very unlikely that we will really have all the facts of the present state of the system, and get that deep an understanding of the laws that regulate it, that we can make complete predictions. In the fact of advertising today, I think, is testimony that we are not completely ignorant of motivation.

Q. We hear a great deal today about the status of the physical scientists in Russia and in a sense are in a contest with them. Would you care to comment on their attitudes and extent of biological experimentation?

A. Yes, biology in the Soviet Union has had a paralyzing blow because of the inquisition which has operated there in the field of genetics. The very mention of DNA was anathema for many years and the notion of the gene as something worth studying at its own level, that had any stability of structure, was politically unacceptable. People who espoused the kind of thinking that I am discussing today were just not allowed to work, and some cases had even more serious consequences. This has had a very serious effect on Russian biology as a whole. Sensible people, when they see there is an area of science which is politically disreputable, just aren't going to go into it. They stayed out of biology in the Soviet Union until very recently. What is saving Soviet biology now is the fact that many of their physicists, as the physicists here, have been taking an interest in the same kinds of problems but they just don't mention the word "heredity". In fact, that is one reason perhaps for the popularity of "molecular biology".

Until very recently, performance in biology in general has been very, very poor. Biochemistry has been very spotty and is the most poorly developed in those areas touching on the more fundamental questions which we have been discussing here. Our Russian colleagues do not lack for brains and once they get themselves out of the organizational mess of handling biology, they are bound to make strides comparable to what they can do in other fields. They are just beginning to.

Q. Would you care to comment on the importance of auto-immunity reactions in disease?

A. Auto-immunity is a breakdown of the normal rules of the game of immunity. Immunity is a relatively recent evolutionary innovation. In the vertebrates, it starts in a rather limited way in the fishes, and it comes to full flower only in the warm-blooded animals. Simpler animals and plants do not have immune mechanisms; somewhere in this late stage of evolution it was discovered how to go about setting up an immune reactive system. After the introduction of a foreign substance into the organism, the right kind of messenger RNA is produced that would make the right string of amino acids that would fold up into the right shape to react to those foreign substances. This system has only evolved because it was of some use to the organism in which it occurred, and obviously some discrimination is needed to form only useful antibodies; these proteins that have folded up into the right shape so that they react only with foreign substances and not those normally present in the organism. Even small changes in the chemical architecture of body proteins can result in reactivity to them. Yet, in the normal course of events, we do not react to our own substances. This has been one of the puzzling starting points of any theories of antibody formation. A lively controversy has developed concerning the way in which the information is passed on to the messenger RNA: "This kind of antibody ought to be produced."

On the instructive theory of antibody formation an arsenic atom could come along, sit in the right place in the cell and mold a protein around it and give the cell the instruction how to make a protein that would react with arsenic. You can substitute any one of many thousands of other substances and get specific antibodies in each one of these. But this does not take account of more recent knowledge of the function of the messenger RNA that controls a sequence of amino acid protein. Well, how in the world do we get other elements into the system? An alternative proposal is in fact to admit the lack of ingenuity of the cell in responding to specific instruction from outside. Admit the general application of the rules of the game that the cell never gets any sequence information from outside its own nucleic acids. The question then becomes how to decide which page from the DNA library to read for instructions on a given antibody. But one's imagination begins to boggle at the idea that there is already stored in *every* cell the information needed to make any one of many hundreds of thousands of alternative kinds of antibodies and that the signal from the arsenic atom is to light the switch that says let's make anti-arsenic antibodies. The alternative answer (the elective theory of antibody formation) calls for a very high rate of mutation of the DNA, a lot of chemical accidents taking place in the DNA of the cells of the lymphoid tissues: lymph nodes, thymus, the spleen, the bone marrow, the tissues responsible for making antibodies. That within the cells of these tissues, the particular patch of the particular segment of the DNA responsible for making globulins is set apart from all other DNA by its very high rate of mutation. This is one way of achieving plasticity of structure. We therefore end up having in our body some ten trillions of cells which have undergone this kind of very random evolution and any one cell only has one or very few patterns of antibody formation available to it. But as a result of this accidental diversification, the totality of cells in the body have some trillions of different potential patterns of antibody formation. Now we can see the role of the antigen; the information that it conveys is not to say you must make a protein that fits me. It asks, "Do you already make a protein that fits me?" And if the answer is "Yes", the instruction that it gives to *that* cell is, "You, the cell, are the one that must proliferate in order to make antibody in order to wipe me out!" That is why I call this an elective mechanism.

Well, how do we take care of auto-immunity? There is no fundamental chemical difference, as a class, between the self, the inside substances, and the outside ones. Only the history of the organism distinguishes them. The substances that have been in the organism from its inception are the self ones, the ones that only came into the picture after the birth of the organism are the foreign ones. The ea.ly introduction of what would have been foreign substances into the embryos of mice during prenatal life made these substances behave as if they were part of the organism. The organism will not then react to them when given later on, as Medawar demonstrated. Within the framework of the elective theory, this would mean that there were two modes of response in this recognition set-up. If this question is asked early in the life of the animal, the result is the destruction of the cell containing those patterns that will react with those substances. If it is asked later on in the life of the animal, the answer is the proliferation of those cells.

We can now see how the mechanism might go wrong. One way is to have substances come into the organism that are part of the organism but have never reached *all* of the lymphoid cells of the animal. This is true of the lens of your eye and is true of some of the proteins in your central nervous system. These are highly insoluble materials, and do not reach the bloodstream. But, if I take an animal eye and extract the lens from it, I can produce antibodies against his own lens in that same animal. According to the elective theory this is because the necessary criteria for identification with self, the early dissemination of the substance throughout all the tissues of the body so as to destroy all the patterns that might react with it, just hasn't taken place. The lens protein has been segregated into that one place and never gets around in the circulation.

Anything that will allow this breakdown, any modification of the rule that says that consistent patterns are going to be destroyed will give the same result. If the pattern is not destroyed by early contact, then you will get the immune reaction. Rheumatic fever and some more exotic diseases such as lupus erythematosus come into the picture; some diseases of the central nervous system are very clearly the result of the sudden availability of proteins that were not normally accessible to the general circulation, perhaps the result of local virus damage; antibodies develop, the wandering cells of the body become sensitized to them and they aggressively seek out places where these substances may be found and may destroy that tissue.

Q. Would you care to comment on possible technological breakthroughs of plant biology.

A. Well, I think there are a couple of places although these have been happening. Of course, the control of the genetic composition of plants has been the technological breakthrough of genetics over the past twenty or thirty years and we have controlled breeding of plants in a way that we have in no other organisms. Connected with plant biology is, of course, the mechanism of photosynthesis and I think we have the expectation that if we wanted to bother, we might use the biochemical model of photosynthesis some time during the next five or ten years. I don't think anybody feels that it is going to be much further along than that. We have all the pieces right now I guess to put it together in a working system, in fact, to work in a test tube. It seems very likely, however, that we'll try and find more direct ways of using solar energy than going through this route.

More directly, I think of plants and of plant tissue cultures as being very rich sources for some of the materials that we are very much interested in—in studies of this kind. We may find it very much to our advantage to be cultivating plants for the production of exotic biochemicals of a much wider range than we do now. Of course, plants include microorganisms, actinonycetes, the antibiotic producers, so we are very much in the middle of that kind of technology. I think the general answer to your question is that I don't visualize dramatic breakthroughs. I visualize a great expansion of present technology in utilizing plant material for the same kind of purposes and we will be doing the same kind of juggling with plant heredity and plant development in order to make better tools for our purposes that I have talked about in animal development. We will probably do it sooner. We will be using them in experimental material, particularly microorganisms because of their immense convenience just as we have been doing all along. I need not dally to mention that most of the work that I have talked about with regard to the functional significance of nucleic acid in protein synthesis has come about from studies in microorganisms.

Q. From the floor. (Unrecorded)

A. The fact is, there is still a raging controversy as to whether the brain is a physical or chemical mechanism. Well, I had better qualify this. We can say the brain does two things: It *stores* information and it *computes* on the information. The storage might be part of an electric circulation; if you stop the circulation of current through the brain, you would lose what was stored in it. But I am rather inclined to think that there is material storage instead, that if we knew how to read it we could take a brain that was only recently living and know what was stored in it. In the same sense that you could take a computer that was unplugged (and if no chemical changes had taken place in transistors, but of course they do) you could just read the chemistry of the existing state of every element of the system and you would know what information was stored in it.

Beyond that, it is just an immense controversy as to whether this storage does involve structural changes, the laying down of synaptic knobs, the diffusion of a few atoms across the transistor-like junction or whether it is entirely a matter of the dynamic reverberation of signals that just keep on going round. I find the latter very difficult to believe, that it can keep going as well as it does over periods of eighty years. There must be some substance, some structure which is formed as the material basis of memory. As to the switching mechanisms, we know just a little bit about it. We know that new ones connect to one another and that an impulse fired off in one neuron can be propagated down its fiber and then can fire another neuron. But only the simplest cases have been studied, and so far only in a rather superficial way for reasons of technical difficulty. One of the things that we are just getting started on in our own laboratory is an attempt to try and extrapolate the techniques and general concepts of molecular biology, which I have been talking about today, into the realm of neuron storage. For example, can we get evidence that there are memory proteins which might be recognized by their having the same metabolic properties as memory?

My own astonishment, in looking into this area, has been how few elementary and obvious experiments have been done, even, for example, of how many neurons there are in the brain and whether this number changes with development and learning.

Q. Is there any likelihood of synthesis of life in the test tube?

A. Oh, I don't think we will want to bother! That is a very complicated set of procedures that you have in mind—if by a living organism you mean something that is really free-living that you can stick inside of a test tube and it will go ahead and multiply. If by free-living you mean something like a virus which does not make very much of the supporting machinery but is capable of undergoing the elementary reactions of self-reproduction, it's quite possible that this has been done already in the kinds of experiments on nucleic acid replication that we have been talking about.

I am trying to think what kind of criteria one would use; you have to define the nutritional inputs into the system as your starting point. If the nutritional input were going to be limited to the usual nutrients that we, or bacteria, eat, then it will take something as complicated as a bacterium to be able to convert those into nucleotide triphosphates, for example, the immediate precursors for DNA. So it means twenty or thirty enzymes that have got to be developed just for that job alone. Probably a hundred or two hundred enzymes are needed altogether just for the surrounds of this problem of converting amino acids into their activated forms, for building up the RNA, etc. That is rather a complicated affair. Do you actually want to take the trouble to build it up yourself piece by piece when there are a lot of organisms around that you can pull apart and put together again—which is what we do now?

Q. Can we now visualize any specific chemical structural basis for a three-letter genetic code, or a two-letter one?

A. Well, the code is basically a three-letter one according to the best information one can get now. There are four possibilities at each position in the sequence so a single nucleotide could code four alternative amino acids but no more. There are twenty. With only two in combination, there are four times four—sixteen—four short of the necessary twenty. In general, you need three and then you have more than enough. Interestingly enough the cell uses more than enough. There seems to be more than one combination of nucleotides which will code for the same amino acid. That means that there are different ways of writing the same ultimate message; in different languages, or different alphabet units used, but they have the same meaning. It is conceivable that we could have a mixed code, that there are some two-letter combinations that are useful. There is no explicit experiment today that would say the code for phenylalanine was UUU, rather than UU; the way the experiments are done doesn't yet give us that kind of resolution. However, other amino acids would have to be coded by three letters and there is the problem of confusion that you would get into if the code were UU for phenylalanine and UUC for serine (which it may be). The problem is telling those two apart, whether to read two letters or three letters at a time. So we are at the point of study where there are details of this kind that are only just now being mopped up. We know there are two or three different alternatives for a few codes—we know some of the redundancy. We are beginning to inquire what use the cell makes of its redundancy. It undoubtedly does make some as there are some kinds of cells that produce an sRNA in response to one code for a given amino acid, others which produce sRNA in response to a different code for the same amino acid.

Q. I wonder if we may come back to the problem of aging for a minute? Could you visualize that aging is nothing really but a slow mutation of some form of DNA?

A. Well, I think that this happens. I don't know how much of aging has this basis. It would take me some time to justify my position and maybe it isn't tenable, but I think the *ultimate* limit to our attack on the aging problem will be cellular aging in the sense that you now speak of, the accumulation of mutations which will make it difficult for the cell to perform its proper functions. But I don't believe that this is the *actual* limit in the total organism as it is now constructed because I can visualize other mechanisms that get in the way of perfectly competent individual cells, so that the system is too crowded—too clogged up to take full advantage of their individual capabilities. It is conceivable that mutation in the DNA of the neuron is the ultimate limitation to how long we can keep the information storage mechanism properly working, for example.

Q. From the floor. (Unrecorded)

A. No, I meant that as a prototype of a number of similar scarring processes and delays in getting rid of the structures, non-living structures that have been introduced earlier which themselves get worn out, but which do clog up the system. If you think how often there must be small vascular accidents, particularly in the central nervous system, it must black out a small patch of tissue, unnoticeable in the individual but in the aggregate eventually adding up to significant impairment. We know this happens. When we get past these scars in the organism, we will then unquestionably reach another limitation of cellular aging.

Q. What are the possibilities of forcing a self-substance to take on the character of external substance? (In immunity.)

A. This experiment can be done in a somewhat artificial way. On the hypothesis that I have mentioned, if you once remove a self-substance from the circulation for a period of time, long enough that new patterns evolve mutationally in the lymphoid system, and then put it back again, it should no longer be accepted as self. I think this is exactly what happens in insulin-resistance in man; e.g., in diabetes, the loss of capacity to produce normal insulin after that protein has disappeared from the system. In the course of subsequent therapy we get immunity to insulin.

Q. From the floor—regarding relation of auto-immunity to cancer.

A. Yes, the thought has been proposed that a breakdown in the mechanism will not only fail to eliminate foreign-type intruders that arise spontaneously, but that there may be in fact some stimulation of cells by immune response to them.